PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 08 February 2001 (08.02.01)	
International application No.: PCT/NL00/00294	Applicant's or agent's file reference: 4/XD58/AMN/15p
International filing date: 08 May 2000 (08.05.00)	Priority date: 05 May 1999 (05.05.99)
Applicant: PAPING, Max, Gregor et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

05 December 2000 (05.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4/XD58/AMN/15p		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL00/00294	08/05/2000	05/05/1999
International Patent Classification (IPC) or national classification and IPC A61B19/04		
Applicant BUDEV MEDICAL B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05/12/2000	03.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schnack, A Telephone No. +49 89 2399 8149

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL00/00294

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-23	as originally filed				
Claims, No.:					
1-26	as received on	06/07/2001	with letter of	05/07/2001	
Drawings, sheets:					
1/1	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6, 10-26
	No:	Claims	7-9
Inventive step (IS)	Yes:	Claims	1-6, 10-26
	No:	Claims	7-9

Industrial applicability (IA)	Yes:	Claims	1-26
	No:	Claims	none

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following document:

D1: US 4 143 109

Section IV
Unity

The present application does not comply with the provisions of Rule 13.1 PCT having regard to unity of invention: The separate inventions are:

Group 1, claims 1-16:

Method for reducing the allergen activity of rubber latex comprising incorporating an amount of starch in the rubber latex and rubber latex as prepared by this method.

Group 2, claims 17-26

Use of starch as donning powder for surgical gloves, characterized in that the starch is granular, low crystalline, preferably non-crystalline starch. Gloves with granular, low crystalline, preferably non-crystalline starch.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons: the use of rubber latex in combination with starch, (i.e. the only common feature of the two inventions) is already known from D1, (see passages mentioned in the search report and the claims). The requisite unity of invention (Rule 13.1 PCT) therefore no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the two mentioned groups of dependent claims.

A search has been carried out for both inventions. Since it appears that the additional effort for establishing an opinion on both inventions is bearable, this opinion is based on both inventions.

Section V

V.1. Novelty

Remarks under Article 33(2) PCT:

Group 1:

The subject matter of group 1 of the present application is based on the finding that allergic reactions towards latex is reduced when an amount of starch is **incorporated into the liquid latex before forming the article**, (cf. present examples). Thus, the term "incorporating an amount of starch in the rubber latex" according to present claim 1 is considered unclear and imprecise, because this term does not unambiguously define how the starch is incorporated into the latex. The claim should contain the process feature **incorporating an amount of starch into the liquid latex before forming the article**. If this feature is included in present claim 1, it appears that novelty of the subject matter according to present claims 1-6 can be acknowledged.

Rubber latex with a amount of starch incorporated therein for use in surgical gloves is known from D1, (see example 1). Thus, the subject matter of present claims 7-9 and 16 lacks novelty in view of D1. However, the subject matter according to present claims 10 and 11 appears to define novel subject matter.

Also present claim 12-15 appear to define novel subject matter in view of the documents cited, because none of these documents appear to teach that the allergen activity of latex can be reduced by incorporating starch into the latex.

Group 2:

D1 discloses the use of starch as donning powder for surgical gloves. In D1, a part of the fluid latex is mixed with cross-linked corn starch and used to cover a preformed latex glove, (see D1, example 1). This is done in order to produce powder free gloves for surgery, thus avoiding granulomas and other postoperative complications caused by powdery starch infecting the wound, (see D1, col. 1, lines 12-26). D1 does not appear to teach to use granular, low or non-crystalline starch. Thus, the subject matter

according to present claims 17-26 appears to be novel with respect to D1.

V.2. Inventive step

Remarks under Article 33(3) PCT:

Group 1:

Present claims 8-13 and 18-21 relate to the use of starch for reducing allergen activity of rubber latex.

The prior art incorporation of starch into latex preparations was done in order to suppress starch powder liberation, (see D1, col. 1, lines 12-26). Thus, the present effect; namely reduced allergen activity of starch incorporated latex, can be considered as a novel and inventive technical effect, because novel applications for this effect can be defined, (e.g. condoms and inflatable balloons).

Thus, the subject matter according to present claims 1-6 and 10-15 appears to involve an inventive step.

Group 2:

The applicant argues that the use of granular, low-crystalline or non-crystalline starch as donning powder for surgical gloves is novel and that the technical effect of using such starch is that this type of starch can be broken down by the body quite easily in contrast to the type of starch used according to D1, thus avoiding granulomas. This effect does not appear to have been described in D1 or in other of the prior art documents cited, for which reason an inventive step appears to be acknowledgeable.

V.3. Industrial applicability

Remarks under Article 33(4) PCT:

The subject matter according to present claims 1-26 fulfil the requirements for industrial applicability.

Section VIII

Remarks under Article 6 PCT:

It is presently not clear whether the distinguishing terms "granular, low crystalline, preferably non-crystalline starch" are in fact clear terms. E.g. how low is "low-crystalline"? And what does the expression "granular starch" cover?

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
4/XD58/AMN/15p		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/NL 00/ 00294	08/05/2000	05/05/1999
Applicant		
BUDEV MEDICAL B.V. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The abstract is changed as follows:

The present invention relates to rubber latex comprising an amount of starch, wich rubber latex has a reduced allergen activity as compared to the same rubber latex without starch.
In addition, the invertion relates to the use of modified starch as donning powder for surgical gloves, wherein the used starch is a granular, low crystalline, preferably a non-crystalline starch

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(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/08584 A1

(54) Title: USE OF RUBBER LATEX IN COMBINATION WITH STARCH

(57) Abstract: The present invention relates to rubber latex comprising an amount of starch, which rubber latex has a reduced allergen activity as compared to the same rubber latex without starch. In addition, the invertion relates to the use of modified starch as donning powder for surgical gloves, wherein the used starch is a granular, low crystalline, preferably a non-crystalline starch.

USE OF RUBBER LATEX IN COMBINATION WITH STARCH

The present invention relates to the use of rubber latex in combination with starch.

Rubber latex is being used for the production of a variety of products, such as surgical gloves, condoms etc. The use of rubber latex has, however, been associated with several drawbacks, such as for example latex allergies in health care personnel wearing rubber latex surgical gloves. These reactions may be due to direct allergic reactions resulting from direct contact of the rubber latex allergens with the skin of the wearer, or may result from inhalation of airborne latex allergens adhered to the starch powder that is commonly used as donning powder for rubber latex surgical gloves. The starch powder itself, when used in surgery, may be left behind in the patient's wound and can, besides the aforementioned hypersensitivity reactions, also lead to the formation of granulomas and adhesions.

The present invention aims to obviate the drawbacks that are associated with the use of rubber latex articles, such as surgical gloves.

It is thus a first object of the invention to reduce the allergen activity of natural rubber latex in order to reduce the incidence of latex allergies.

It is another object of the present invention to provide a donning powder for rubber latex surgical gloves which is easily absorbed by body tissues and thus does not give rise to granuloma formation and adhesions when introduced into the body.

These objects are achieved by the present invention by the use of rubber latex in combination with starch.

The present invention thus relates to rubber latex with a reduced allergen activity, to a method for

preparing said rubber latex, and to medical and non-medical articles comprising said rubber latex.

Natural rubber latex is processed almost exclusively from the sap of the Hevea Brasilliensis tree (>99%), which is commonly found in Africa and Southeast Asia. Rubber workers collect the sap, a milky white dispersion known as liquid latex, by cutting deep strips into the bark of the tree. The liquid latex is an emulsion of rubber particles (cis-1,4,-polyisoprene) with diameters ranging from 5 nm to 3 μm (<d> = 0.25-0.8 μm) in an aqueous serum. The rubber particles are coated with a negatively charged layer of proteins, lipids and phospholipids that provide the structural integrity and stability of the dispersion.

For the manufacture of natural rubber products, such as latex rubber gloves, the starting material is the concentrated latex. The gloves are manufactured by dipping porcelain or glass moulds into the liquid latex. This can be achieved by dipping the moulds in a coagulating salt (calcium alginate) and then dipping them into a prevulcanized latex concentrate, yielding film thicknesses between 0.2 and 0.8 mm, or by dipping the moulds several times in the latex, and crosslinking the gloves afterwards. In the second method the films are not allowed to dry completely between dips in order to ensure homogeneous film formation. One dip accounts for approximately 0.05 mm. The final rubber product contains 93-96% polyisoprene and up to 3% protein by weight.

As a consequence of the increasing use of natural rubber articles, such as for example surgical gloves, the occurrence of latex allergy in hospital personnel and patients has become a major problem. Thus, more and more people are using surgical or examination gloves made from natural rubber latex containing a high level of proteins, which are the cause of the latex allergies. In particular, health care personnel and patients have shown a growing sensitivity to natural rubber products. The current estimate of healthcare

workers being allergic to natural rubber gloves ranges between 10 and 20%. This phenomenon has been attributed to the recent dramatic rise in the use of latex gloves by medical, dental and auxiliary personnel for the protection against AIDS and hepatitis viruses. Although the allergic reactions are most obvious with respect to natural rubber gloves, a large number of other natural rubber articles are on the market, like balloons, condoms, footwear, clothing, adhesives, carpet backing etc. resulting in latex allergies as well. The problem of sensitivity to latex is therefore not restricted to (surgical) gloves.

The clinical manifestations of immediate hypersensitivity to latex usually arise from direct contact with natural rubber, but may also result from inhalation of airborne latex allergens. The symptoms and signs may be localized or generalized urticaria (development of wheals, flares and hives), angioedema, rhinitis, conjunctivitis, asthma, tachycardia and/or anaphylactic shock (increased heart beat rate, lowered blood pressure and possible loss of consciousness).

Allergy to latex is a typical example of an immunologically-mediated immediate hypersensitivity reaction, which is induced by allergenic proteins in the latex and is mediated by IgE antibodies. This reaction is known as a Type I allergy.

There are over 240 polypeptides in natural rubber latex, as detected by two dimensional electrophoresis. The protein concentration of a native latex sap was reported to be 16.53 mg/ml. A quarter of these proteins is associated with the rubber particles, while the rest is present in the non-rubber fractions. The number of allergenic polypeptides/proteins identified as allergens (in humans) ranges from 11 to 57.

A number of allergenic proteins have recently been detected in latex sap, ammoniated latex and extracts of rubber gloves. Thus, a trypsin-sensitive allergen was demonstrated with a molecular weight around 30 kDa. In

addition, it has been found that the Rubber Elongation Factor (REF = 58 kDa), which plays an important role in the polymerization of the polyisoprene chains, is a major allergen in latex. Of the major allergen prohevein (20 kDa) and the prohevein C-domain (14 kDa) it was found that its N-terminal 43-amino acid fragment hevein carries the main IgE-binding epitope. Hevein is the most predominant protein in natural rubber latex and has chitin binding properties. A 23 kDa polypeptide, which shows some amino acid sequences similar to the REF also shows allergen activity. Furthermore, lysozyme (27 kDa), which is related to the defense-related proteins in rubber latex, a 46 kDa and a 36 kDa protein are found to be allergens.

The latex proteins are believed to dissolve in the body sweat inside the gloves and are then absorbed through the skin. The onset of latex sensitization is insidious in nature and is progressive. It occurs slowly, sometimes over a period of many years, as the body is repeatedly exposed to latex and develops an immunologic memory to the proteins. The presence of latex specific IgE antibodies in the bloodstream precedes the development of clinical symptoms by months or years. It is not known what level of protein is required to actually sensitize an individual. Because of this no regulation exists for limiting the amount of allergenic protein that a product may contain.

In addition, most latex gloves are manufactured with a corn starch powder to facilitate donning. The allergenic proteins adhere to the donning powder, which may become airborne when the gloves are snapped on and off. As a result many healthcare workers inhale the protein-laden powder over a period of several years and thus may develop latex sensitivity.

Chemicals which are added to the latex prior to processing may also cause a severe rash and irritation. However, reaction to these chemicals is most commonly a

Type IV allergy. Symptoms for Type IV allergy develop within 24 to 72 hours of exposure.

In order to measure the sensitivity to latex a number of allergy tests are available. The most reliable test is the skin prick test, in which a person is exposed to latex or latex extract via contact with the skin. Afterwards the reaction of the exposed skin is monitored. The latex RadioAllergoSorbent Test (RAST) is available for the in vitro detection of latex IgE antibodies (Latex, k82, Pharmacia Diagnostics), but is less sensitive than skin prick tests. In addition, a new latex-specific fluorescent enzyme immunoassay for the detection of latex specific IgE antibodies has been brought on the market (Pharmacia CAP System, PCS).

The in vitro assays show considerable variation in the total protein and allergen content of different glove brands. Furthermore, the amount of protein eluting from a glove depends on the method used and does not always correlate with the allergenicity in skin prick tests, indicating that the total protein measurement is not a sufficient method to monitor the allergenic properties of latex gloves.

In an attempt to reduce the allergenic effect of the allergens in gloves, the gloves are run through a chlorine wash process, known as leaching, after they are dipped and dried, to remove the proteins which are responsible for the allergic reactions. However, in efforts to speed up production and meet increasing demands, glove manufacturers may fail to adequately wash the gloves. Steam sterilization of the gloves further decreases the protein level.

The activity of allergens in latex can also be reduced by treatment with an alkaline potassium hydroxide solution. However, to reduce the allergenic effect of the latex an extra step in the production process is needed. In addition, the gloves will be more costly.

Another option is the use of latex-free gloves. These gloves can be made of neoprene, styrene butadiene

block copolymer or styrene ethylene butadiene styrene block copolymer. However, these non-latex gloves often have inferior barrier properties and often are found to lack the comfort and fit of natural rubber latex gloves. Furthermore, they are less environmental-friendly as the energy required to produce them is 7-11 times more than is the case of natural rubber and they are generally not biodegradable. In addition, except for vinyl, the synthetic gloves are more costly.

Alternative methods to remove or inactivate the allergens in the latex are described in US 5,563,241 in which the rubber latex is contacted with an anion exchange resin. Subsequently, the protein-resin complex is removed from the latex. US 5,691,446 relates to a method of dipping the dried rubber product in a chemical substance that inactivates the allergens on the surface. Again, extra steps are needed for the manufacturing of latex articles. In US 5,777,004 proteases are added to the liquid latex for denaturation of the allergenic proteins. These proteases, however, may be the cause of allergic reactions themselves.

As a result of the high incidence of latex allergies the use of latex articles, such as surgical gloves, has been restricted or even banned from hospital environments, indicating the significance and impact of the problem of latex allergies.

In the research that led to the present invention the effect of incorporating starch in rubber latex was investigated. It has thus been shown that by incorporating a small amount of starch in the rubber latex the allergen activity of said rubber latex can be reduced. The starch can form both physical and chemical bonds with the amino and acid groups of the proteins, thus binding potentially allergenic proteins.

Sources for the starch as used in the invention are starch preparations, which generally comprise starch and a small amount of other constituents, such as

proteins. According to the present invention, preferably low-protein, colloidal starches are used.

According to the invention, the "allergen activity" of rubber latex refers to the amount of water-soluble allergens in extracts made from said rubber latex. Thus, in order to measure the allergen activity of rubber latex, extracts are made from rubber latex samples (as described in Example 1) and the amount of water soluble-allergens in these extracts is determined using a Latex Elisa for Antigenic Proteins (LEAP) test (Beezhold, The Guthrie Journal 61, 77-81, 1992). It has been shown that by adding small amounts of starch the allergen activity of the latex rubber samples (i.e. the amount of water-soluble allergens in a rubber latex extract) is significantly decreased as compared to the same rubber latex without starch, thus resulting in a reduced incidence of allergic reactions in persons contacting said rubber latex.

Comfort tests have shown that the use of starch concentrations of less than 10 w% do not have a negative effect on the mechanical properties of the samples. When more starch is added, the rubber samples are too stiff in order to be used in rubber articles, such as gloves.

According to a preferred embodiment of the present invention, the rubber latex comprises an amount of starch for reducing the allergen activity of rubber latex such that the allergen activity of said rubber latex is maximally 50%, preferably maximally 40%, more preferably maximally 30%, most preferably maximally 25% of the allergen activity of rubber latex without starch, as measured by a latex ELISA for antigenic proteins.

In particular, according to the present invention the rubber latex preferably comprises an amount of starch for reducing the allergen activity of rubber latex such that the allergen activity of said rubber latex is maximally 20%, preferably maximally 15%, more preferably maximally 10%, most preferably maximally 5% of the allergen activity of rubber latex without starch, as

measured by a latex ELISA for antigenic proteins. The allergen activity of the rubber latex according to the invention thus is significantly reduced as compared to the currently used rubber latex without starch.

Preferably, the used starch is a modified starch. Methods for obtaining modified starch are for example described by Wurzburg (in: Modified starches: Properties and Uses, 1986; CRC Press Inc, Eds, Bocaraton, Florida, USA). However, according to the invention modified starch is preferably obtained by gelatinizing the starch in an extruder, and crosslinking the starch with glyoxal as described in the co-pending European patent application No. 99200203.0 and Example 1 of the present application. Particles of the modified starch (100-200 nm) are dispersed in water to obtain a 10 w% dispersion, which is then mixed with liquid rubber latex.

According to the present invention various starches can be used, such as for example potato starch, Tapioca, waxy corn starch and waxy rice starch.

The invention further relates to a method for reducing the allergen activity of rubber latex comprising incorporating an amount of starch in the rubber latex. In particular, the invention relates to a method for reducing the allergen activity comprising incorporating an amount of starch in the rubber latex such that the allergen activity of said rubber latex is maximally 50%, preferably maximally 40%, more preferably maximally 30%, most preferably maximally 25% of the allergen activity of rubber latex without starch, as measured by a latex ELISA for antigenic proteins.

According to a particularly preferred embodiment of the invention the method for reducing the allergen activity of rubber latex comprises incorporating an amount of starch in the rubber latex such that the allergen activity of said rubber latex is maximally 20%, preferably maximally 15%, more preferably maximally 10%, most preferably maximally 5% of the allergen activity of

rubber latex without starch, as measured by a latex ELISA for antigenic proteins.

The fact that the method according to the invention involves low material costs and can be easily implemented in the existing glove manufacturing processes, without significant investments, is an important advantage of the present invention.

Furthermore, the invention relates to rubber latex articles, such as surgical gloves, condoms, inflatable balloons etc., comprising the rubber latex of the invention, wherein at least the surface contacting the skin of the user is fabricated from the modified rubber latex.

The invention further relates to the use of starch for reducing the allergen activity of rubber latex, and to the use of the rubber latex according to the invention for the manufacture of rubber latex articles.

By using the rubber latex of the present invention for the manufacture of rubber latex articles the incidence of allergic reactions to latex can be significantly reduced. This is particularly important for health care personnel, such as dental, medical and auxiliary personnel, as they are at the highest risk for developing severe latex allergies.

The present invention further relates to the use of a modified starch as donning powder for surgical gloves, and to a surgical glove provided with said modified starch as donning powder.

In the process of making surgical or examination gloves a mould of glass or ceramic is dipped in a concentrate of liquid natural rubber latex. After drying, the resulting rubber product remains a little sticky. In order to reduce this stickiness generally a starch powder is applied to the gloves after manufacturing.

Starch (mostly corn starch), which absorbs humidity, thus is the main constituent of glove powder.

When used in surgery, it is possible that some of this corn starch powder is left behind in the patient's wound. This would not be a problem if the starch were completely absorbed by the body. However, it has been shown that residual starch can lead to the formation of granulomas and adhesions. These granulomas are caused by foreign particles which cannot be broken down in the body and form adhesions. When the damaged tissue is investigated with an optical microscope with crossed polarisers a Maltese cross is observed, typical for the presence of starch granules.

To prevent the formation of starch powder granulomas after operation it is known to remove all traces of the starch powder from the glove. However, in order to obtain totally powder free gloves the gloves have to be rinsed intensively with chemical compounds, which is both time-consuming and expensive.

It is also known to use non-powdered gloves in order to reduce the incidence of starch granulomas and adhesions. Several non-powdered gloves are on the market, and the lubrication of these gloves is obtained by a variety of methods, ranging from hydrogels to multilayer systems. However, these non-powdered gloves are far more expensive (about 3 times) than the powdered ones. In addition, non-powdered gloves are thicker and thus less comfortable to wear than powdered gloves. They are more slippery, more difficult to don (the hands must be totally dry) and have a worse grip on the instruments. According to the present invention it has been found that by the decrease of crystallinity of the modified starch according to the invention granuloma and adhesion formation due to starch contamination of body tissues can be reduced.

Initially, surgical gloves were sterilized by means of autoclaving. The replacement of this technique by gamma sterilization resulted in a dramatic increase of case reports of starch granulomas. It has been shown that autoclaved starch was almost completely absorbed from the

peritoneal cavity of a rat within a period of 48 h, whereas irradiated starch was still not fully absorbed after 70 days. Scanning electron microscopy indicated that autoclaved starch showed pitting and cracking of the granule surface, while irradiated starch showed a smooth surface. It was therefore concluded that autoclaving damaged the starch in such a way that rapid absorption occurs.

Native starch is normally deposited in roots, tubers, grains etc, as semi-crystalline granules. It is known from the literature that the amorphous (non-crystalline) parts of the starch granules are easily attacked by the amylase enzymes which are present in saliva and blood. In contrast, the crystalline parts of the granule, which are more ordered and dense, are not very sensitive to enzymatic attack. For this reason, the semi-crystalline starch granules, if introduced in the human or animal body, are likewise not sensitive to enzymes, and are therefore not easily absorbed by the body tissues.

In the research that led to the present invention it has been found that in order to be suitable as donning powder for rubber gloves, the starch powder should have a suitable particle size (<50 μm). Starch having larger particles, like thermoplastic starch pellets, should be ground which will increase the price of the powder. In addition, the low- or non-crystalline starch should be spherical or oval shaped in order to preserve the lubrication properties. This means that the best shape is the granular form of unmodified starch.

According to a preferred embodiment of the present invention, the modified starch thus is a granular, low crystalline, preferably non-crystalline, starch. The granular, low-crystalline modified starch preferably has a so-called V-type crystal structure.

Methods for reducing the crystallinity of starch are known, based on the gelatinisation of starch with water or glycerol at elevated temperatures, or by

increasing the pH by using NaOH. Such methods for the preparation of granular non-crystalline starch are for example described in US 3,617,383, US 4,465,702, and US 4,634,596, which relate to a method for the preparation of cold water swelling starches. This method is based on mixing the granular, crystalline starch with water and a non-solvent for the starch, such as methanol or ethanol, and heating the slurry to temperatures between 140 and 180°C at elevated pressures. An alternative method has been described in US 5,037,929 wherein the alcohol is substituted by a polyhydric alcohol, like propanediol or glycerol. The temperature can thus be reduced to 100-120°C and an atmospheric pressure can be applied. In US 5,057,157 granular cold water swelling starch is obtained by alcoholic/alkali treatments at ambient temperatures and pressures. These procedures result in the formation of V-type crystals or to an amorphous starch structure. The application of modified starch as a donning powder for rubber gloves has, however, not been described before.

In the research that led to the present invention five different types of starch were modified using a heat and/or alkali treatment in order to reduce the crystallinity in the granules. Two of the used modification methods were already described in the literature. In a third method only water and a sodium hydroxide solution was used. These methods are further described in Example 2.

The modified starches were characterized by optical microscopy with crossed polarizers for the measurement of birefringence (indicating the presence or absence of crystallinity). In addition, the amount and type of crystallinity was determined by X-ray diffraction. It was found that all three modification methods reduced the crystallinity, or even completely eliminated the crystalline structure of the starch granules.

According to a preferred embodiment of the present invention the birefringence of the modified

starch is less than 30%, preferably less than 20%, more preferably less than 10%, and most preferably less than 5% of native starch.

Furthermore, it has been found that the starch powder should not be completely soluble in cold water, because this would cause the gloves to become too sticky and reduce the wearing comfort. For these reasons, the use of thermoplastic starch or lower molecular carbohydrates like maltodextrines is eliminated. According to a preferred embodiment of the invention preferably less than 75% of the modified starch is soluble in cold water.

Preferably, the modified starch according to the present invention is derived from native potato starch, native corn starch, native rice starch, or waxy corn starch.

The modified starch of the present invention is preferably used as a donning powder for rubber latex gloves, so called surgical gloves. Such gloves may however also be used for various other medical and non-medical applications.

The invention further relates to a surgical glove provided with modified starch as a donning powder at least on the surface of the glove to be contacting the skin of the user. To provide a surgical glove with the modified starch, different known methods of powdering the gloves may be used.

The invention will further be illustrated by the following examples and figure.

In figure 1 the results of the X-ray diffraction measurements of the modified starches are visualized.

EXAMPLES

EXAMPLE 1

Preparation of the rubber latex of the invention

A concentrated natural rubber latex was delivered in a drum with a total solid content of approximately 62%, which was modified by the incorporation of a modified strach as allergen-reducing compound.

The starch was a modified native potato starch. An extruder was used to gelatinise and crosslink the starch with glyoxal. A mixture of potato starch and glycerol (87:13) was fed into a twin screw extruder. After gelatinisation, a crosslinker (1-4 w% glyoxal) was injected and the starch was crosslinked. The extrudate thus obtained was dried, ground and dispersed in water, resulting in a 10% dispersion of starch particles (100-200 nm). The liquid latex was mixed with the starch dispersion. The weight fraction of the starch in the dried sample ranged from 0-30%. Fractions of 1-2% gave however the best results.

After the compounds were mixed, test tubes were dipped in the latex for the production of latex specimens. The number of dips ranged between one and four, and the drying temperature was 50°C. After preparation, the dried rubber samples were powdered with native cornstarch in order to reduce the stickiness of the rubber.

Sample characterization

As described earlier, natural rubber latex specimens were made by dipping test tubes in the liquid rubber latex of the invention. This resulted in condom shaped rubber samples (samples: NR00S, NR01S, NR02S).

Since the addition of starch may modify the mechanical properties of the rubber, it was investigated whether the elasticity and strength of the modified

rubber was changed after the incorporation of the starch. In addition, both total protein content and allergen content of the samples were determined.

The total amount of soluble proteins was measured using turbidity measurements. A 10% (w/v) extract was made from small pieces cut from the rubber samples in a phosphate buffer with 0.03% HSA and 0.5% phenol. After one hour of shaking, the extracts were centrifuged for 10 min. at 2000g. The supernatant was filtered over a Millipore 0.22 μm filter. The extracts were stored at -22°C. A small amount of the extract was preincubated in an alkaline solution containing EDTA. Benzethonium chloride (Boehringer Mannheim U/CSF) was then added, producing a turbidity which was read at 505 nm.

The amount of water-soluble allergenic proteins in the rubber latex extracts was determined using the Latex ELISA for Antigenic Proteins (LEAP) as used in the Allergology department of the Academic Hospital of Rotterdam (Beezhold, The Guthrie Journal 61, 77-81, 1992).

Results

Wearing comfort:

The comfort tests showed that after addition of starch to the rubber latex, the elasticity of the dipped samples was reduced. This increment of the stiffness was most notable for samples having a starch content higher than 10%. The elasticity modulus of the 10% starch-latex samples was three times higher than that of the non-modified ones. Furthermore, the surface of the samples became less smooth with increasing starch load. From this it was concluded that the mechanical properties of the samples having a starch load up to 10% were comparable to the non-modified samples.

Protein content:

In table 1 the results of the addition of 1 and 2 % of modified potato starch are shown. From this table it can be concluded that the total amount of soluble proteins did not depend on the amount of starch added. This seems strange, since a dilution effect should be expected. However, the majority of measured proteins originate from the 0.03% HSA in the phosphate buffer. Furthermore, it is known that the starch preparation which is used itself also contains a small amount of proteins. In addition, it is also not inconceivable that the starch absorbs proteins in the liquid latex and thus induces an enhanced protein content in the final samples.

Table 1: Results of the comfort, protein and allergen tests on the modified natural rubber samples

sample	starch w%	dips	weight (g)	com-fort	protein (g/l)	allergen (µg/ml)
NR00S1	0	1	0.54	+	0.31	1.77
NR00S_2	0	2	0.74	+	0.32	2.15
NR00S_3	0	3	1.02	+	0.33	1.42
NR01S_1	1	1	0.26	+	0.32	0.66
NR01S_2	1	2	0.69	+	0.34	0.77
NR01S_3	1	3	0.90	+	0.33	0.44
NR02_1	2	1	0.32	+	0.32	0.38
NR02_2	2	2	0.60	+	0.33	0.74
NR02_3	2	3	0.95	+	0.32	4.31
Romed Baxter Nu Tex Biogel Comform						> 5.4

Allergen activity:

The most significant results of the sample characterisation are listed in the last column of table 1. In this column the allergen concentrations in µg per ml extract are given. The numbers >5.4 indicate that the allergen content is too high to be measured accurately using the method described earlier.

When the 1 % and 2% starch samples were compared to the 0% sample, a decrease in the amount of water-soluble allergens of 60-75% was observed. This indicates that the addition of small amounts of starch to the liquid rubber latex before processing reduced the

allergen activity of the rubber latex of the invention to maximally 25% to 40% of the allergen activity of rubber latex without starch. The allergens are absorbed at the surface of the starch particles which are subsequently fixed in the rubber matrix, resulting in a decrease of the allergen activity of natural rubber latex.

In the last row of table 1, the results of five different brands of glove are listed. The allergen content of all five brands exceeds 5.4 µg/ml extract. This means that even the 0% starch sample gave better results than the commercial brands. This may be due to the industrial processing of the gloves. The samples as described in this example were dried at 50°C. It is possible that this drying step already partly denaturises the allergenic proteins.

EXAMPLE 2

Preparation of modified starch powder

The starch preparations which were used were native potato starch (PN), native corn starch (CN) and native rice starch (RN). Native means that the starches have not undergone any modification prior to use. One waxy starch was used, viz. waxy corn (WC). This starch contains a high amount of amylopectin (>99%) and hardly any amylose. A pregelatinised starch (flocgel) was also incorporated in the measurements. This starch was ground after modification in order to obtain small particles possibly suitable for glove powdering.

As solvents water, glycerol and denaturated ethanol were used. A 1M solution of sodium hydroxide in water was used to increase the pH and provoke gelatinisation of some of the starches.

Three different methods for the preparation of the modified starch were used:

1. In a first method 10 g starch was added to a mixture of 38.8 g glycerol and 11.6 g water in an Erlenmeyer flask. The Erlenmeyer flask was put into a

paraffin bath and heated to 130-140°C. The mixture was homogenised by a magnetic stirrer. After about 5 min, the viscosity of the slurry increased, at which time the Erlenmeyer was retrieved from the paraffin bath and cooled down to 100°C and about 100ml of ethanol or of an ethanol/glycerol (1:4) mixture was added. The slurry was stirred until a homogeneous mixture was obtained. This mixture was suction filtered, after which the solid mass was redispersed in ethanol in order to remove the water. This was repeated. The powder thus obtained was dried at 50°C. This method has been described in US 5,037,929.

2. In a second method the same amounts of glycerol and starch were mixed with 10 g 1M NaOH solution. The paraffin bath was set on 120°C, which resulted in a temperature of the slurry of 100°C. After 5 min, the slurry became more viscous and the Erlenmeyer flask was removed from the heat source. Hydrochloric acid was added in order to neutralise the mixture. The viscous paste was washed with 100 ml of ethanol or ethanol/ glycerol (1:4) and suction filtered. Subsequently, the powder was washed twice with ethanol and dried at 50°C.

3. In the third method 50 g of water was mixed with 5 g starch in an Erlenmeyer flask. A 1M NaOH solution was added slowly into the mixture to ensure an overall concentration of 0.2M NaOH (=13g 1M NaOH). After the viscosity had increased, 100 ml ethanol was added to the slurry. This mixture was stirred and homogenised, and hydrochloric acid was added to neutralise the mixture. The powder obtained after suction filtration was immersed twice in ethanol and dried at 50°C.

The powder which was obtained by these methods was sieved over a 90 μm sieve.

Characterization of the modified starch powder

The powders were characterised by their behaviour in cold water and examined under an optical microscope with crossed polarisers (Zeiss Axioplan).

Furthermore, the amount and type of crystallinity was determined using X-ray diffraction (Philips PW3710).

The soluble fraction of the powder was obtained by mixing 0.1 g of modified starch with 5 g of cold water in a small polystyrene container. The mixture was stirred and put aside at room temperature for 24 hours, and stirred every hour for the first 5 hours. After 24 hours a layer of gelled and unmodified particles sedimented on the bottom of the container. This layer was separated from the clear liquid above, dried in a vacuum oven at 50°C and weighed.

Since all the granulomas formed after starch contamination of body tissue showed a Maltese cross, the modified powder was also subjected to a birefringence test. The amount of particles which still showed birefringence, even after modification, was determined using an optical microscope. The modified starch was immersed in water and put between crossed polarisers. The unchanged particles showed a yellow and blue cross, whereas of the modified particles only the contours were visible. The absence of the Maltese crosses indicated a loss of original crystallinity.

X-ray diffraction was used in order to obtain information about the amount and type of residual crystallinity. Radiation from a Cu K-α source was reflected by the sample and detected by a detector, moving from $2\theta = 4^\circ$ to $2\theta = 40^\circ$. The various types of crystal structures were distinguished by their peak positions. The double helical amylopectin structures are indicated by A, B and C crystallinity, and the single helical amylose by V crystals.

Specimens of non-crosslinked natural rubber were dusted with the modified starch in order to determine whether the powder is applicable as a glove lubricant or not. The dusted rubber was tested for comfort and lubricity. The surface was wetted with cold water and tested for stickiness. Powder, which becomes very sticky is not very suitable as a lubricant.

The results of the sample preparation and material characterisation are listed in table 2. From this table, it can be concluded that the degree of solubility and amount of residual birefringence (birefr.) depends on the modification method used. The highest fraction of starch soluble in cold water is derived by a treatment with a high concentration of NaOH. The source of starch does not play a very important role. However, the waxy type, having a high amylopectin fraction, is less sensitive to the modification. The waxy starch was used in order to prevent recrystallisation of the amylose after gelatinisation of the original starch granules.

Table 2

Starch[a]	Method	solv.[b]	solubility %	Birefr. %	Cryst-.type[c]	comfort[d] wet behaviour
PN	-	-	0	100	B	+, N
CN	-	-	0	100	A	+, N
RN	-	-	0	100	A	+, N
PN1	1	eth.	45-50	5-10	V	+/-, S
CN1	1	eth.	35-40	5-10	V	+, N
RN1	1	eth.	35-40	1-5	V	+, N
PN2	2	eth.	40-45	5-10	V/Am	+, S
PN3	3	eth.	75-80	1-5	Am	+, S
WC2	2	eth./ glyc.	60-65	20-30	A/Am	+, N
Floc-gel	-	-	100	0	Am	-, V

[a] PN: Native potato; CN: Native corn; RN: Native rice; WC: Waxy corn; high amylopectin content; Flocgel: Gelatinised and ground starch; [b] Eth: Ethanol, Glyc: Glycerol
[c] Am: Amorphous; [d] N: Not sticky; S: Slightly sticky; V: Very sticky; +: Good comfort; +/-: Reasonable comfort; -: Bad comfort.

In figure 1 the results from the X-ray measurements are shown. In this figure, the different curves are vertically shifted 500 counts. It can be seen that the crystallinity of the native starch sources (PN, CN, RN) is high and can be divided into an A and B type crystallinity. The potato, corn and rice starches, modified according to method 1 (PN1, CN1, RN1) all gave a similar X-ray pattern, viz. V-type crystallinity. This is indicated by the peaks at $2\theta \approx 14$ and 20°. The two potato

starches treated with NaOH (PN2 and PN3) showed a very low crystallinity. The diffraction pattern for an amorphous starch structure was visible for PN3 (obtained by method 3). Flocgel showed an amorphous X-ray pattern indicating the absence of residual crystallinity. Finally, the crystallinity of the waxy starch was reduced considerably. It was clear that no V-type crystallinity was formed, since the peaks at $2\theta \approx 14$ and 20° were absent.

The behaviour of the powder when applied to the sticky surface of non-crosslinked natural rubber was diverse. The granular starches reduced the stickiness of the gloves. The results of the potato starch were slightly less smooth, due to the larger granule size. Dusting the rubber surface with Flocgel did not result in a smooth surface, because the particles obtained by grinding the gelatinised starch were too coarse.

After wetting the dusted surfaces the stickiness was again tested. The Flocgel became very sticky, because the powder dissolved almost completely in cold water. The modified potato starches (PN1, PN2 and PN3) showed a slight stickiness. The waxy starch and corn and rice starch did not show an enhanced stickiness. Comparing these findings to the results of the solubility measurements, it is obvious that the amount of soluble material in the dusting powder has a large influence on the wet behaviour. The solubility, and thus the stickiness, can be reduced by crosslinking the powder before or after modification. In this way the soluble chains are incorporated in the granules.

CLAIMS

1. Use of rubber latex in combination with starch.

2. Rubber latex as claimed in claim 1 comprising an amount of starch, which rubber latex has a reduced allergen activity as compared to the same rubber latex without starch.

3. Rubber latex according to claim 2 **characterized in that** the rubber latex comprises an amount of starch for reducing the allergen activity of latex such that the allergen activity of said rubber latex is maximally 50%, preferably maximally 40%, more preferably maximally 30%, most preferably maximally 25% of the allergen activity of rubber latex without starch, as measured by a latex ELISA for antigenic proteins.

4. Rubber latex according to claim 2 or 3 **characterized in that** the rubber latex comprises an amount of starch for reducing the allergen activity of latex such that the allergen activity of said rubber latex is maximally 20%, preferably maximally 15%, more preferably maximally 10%, most preferably maximally 5% of the allergen activity of rubber latex without starch, as measured by a latex ELISA for antigenic proteins.

5. Rubber latex according to claim 2, 3 or 4 **characterized in that** the starch is a modified starch.

6. Rubber latex according to claim 5 **characterized in that** the modified starch is obtainable by gelatinising the starch in an extruder and subsequently crosslinking the starch with glyoxal.

7. Rubber latex according to any of the claims 2-6 **characterized in that** the starch is potato starch, Tapioca, waxy corn starch or waxy rice starch.

8. Method for reducing the allergen activity of rubber latex comprising incorporating an amount of starch in the rubber latex.

9. Method according to claim 8 **charact riz d in that** the amount of starch that is incorporated in the

rubber latex is such that the allergen activity of said rubber latex is maximally 50%, preferably maximally 40%, more preferably maximally 30%, most preferably maximally 25% of the allergen activity of rubber latex without starch, as measured by a latex ELISA for antigenic proteins.

10. Method according to claim 8 or 9 **characterized in that** the amount of starch that is incorporated in the rubber latex is such that the allergen activity of said rubber latex is maximally 20%, preferably maximally 15%, more preferably maximally 10%, most preferably maximally 5% of the allergen activity of rubber latex without starch, as measured by a latex ELISA for antigenic proteins.

11. Method according to claim 8, 9 or 10 **characterized in that** the starch is a modified starch.

12. Method according to claim 11 **characterized in that** the modified starch is obtainable by gelatinising the starch in an extruder and subsequently crosslinking the starch with glyoxal.

13. Method according to any of the claim 8-12 **characterized in that** the starch is potato starch, Tapioca, waxy corn starch or waxy rice starch.

14. Rubber latex article comprising rubber latex according to claims 2-7, wherein at least the surface contacting the skin of the user is fabricated from the said rubber latex.

15. Rubber latex article according to claim 14 **characterized in that** the article is a surgical glove.

16. Rubber latex article according to claim 14 **characterized in that** the article is a condom.

17. Rubber latex article according to claim 14 **characterized in that** the article is an inflatable balloon.

18. Use of starch for reducing the allergen activity of rubber latex.

19. Use according to claim 18 **characterized in that** the starch is a modified starch.

20. Use according to claim 19 **characteriz d in that** the modified starch is obtainable by gelatinising the starch in an extruder and subsequently crosslinking the starch with glyoxal.

21. Use according to any of the claims 18, 19 or 20 **characterized in that** the starch is potato starch, Tapioca, waxy corn starch or waxy rice starch.

22. Use of rubber latex according to any of the claims 2-7 for the manufacture of rubber latex articles.

23. Use of starch as claimed in claim 1 as donning powder for surgical gloves.

24. Use as claimed in claim 23 **characterized in that** the starch is a modified starch.

25. Use according to claim 24 **characterized in that** the modified starch is a granular, low crystalline, preferably non-crystalline, starch.

26. Use according to claim 25 **characterized in that** the low-cristalline starch has a V-type crystal structure.

27. Use according to claim 24, 25 or 26 **characterized in that** the birefringence of the modified starch is less than 30%, preferably less than 20%, more preferably less than 10%, and most preferably less than 5% of native starch.

28. Use according to any of the preceding claims 23-27 **characterized in that** less than 75% of the modified starch is soluble in cold water.

29. Use according to any of the preceding claims 23-28 **characterized in that** the modified starch is modified potato starch, modified corn starch, modified rice starch, or modified waxy corn starch.

30. Surgical glove provided with modified starch as a donning powder at least on the surface of the glove to be contacting the skin of the user.

31. Surgical glove according to claim 30 **characteriz d in that** the modified starch is a granular, low crystalline, preferably non-crystalline, starch.

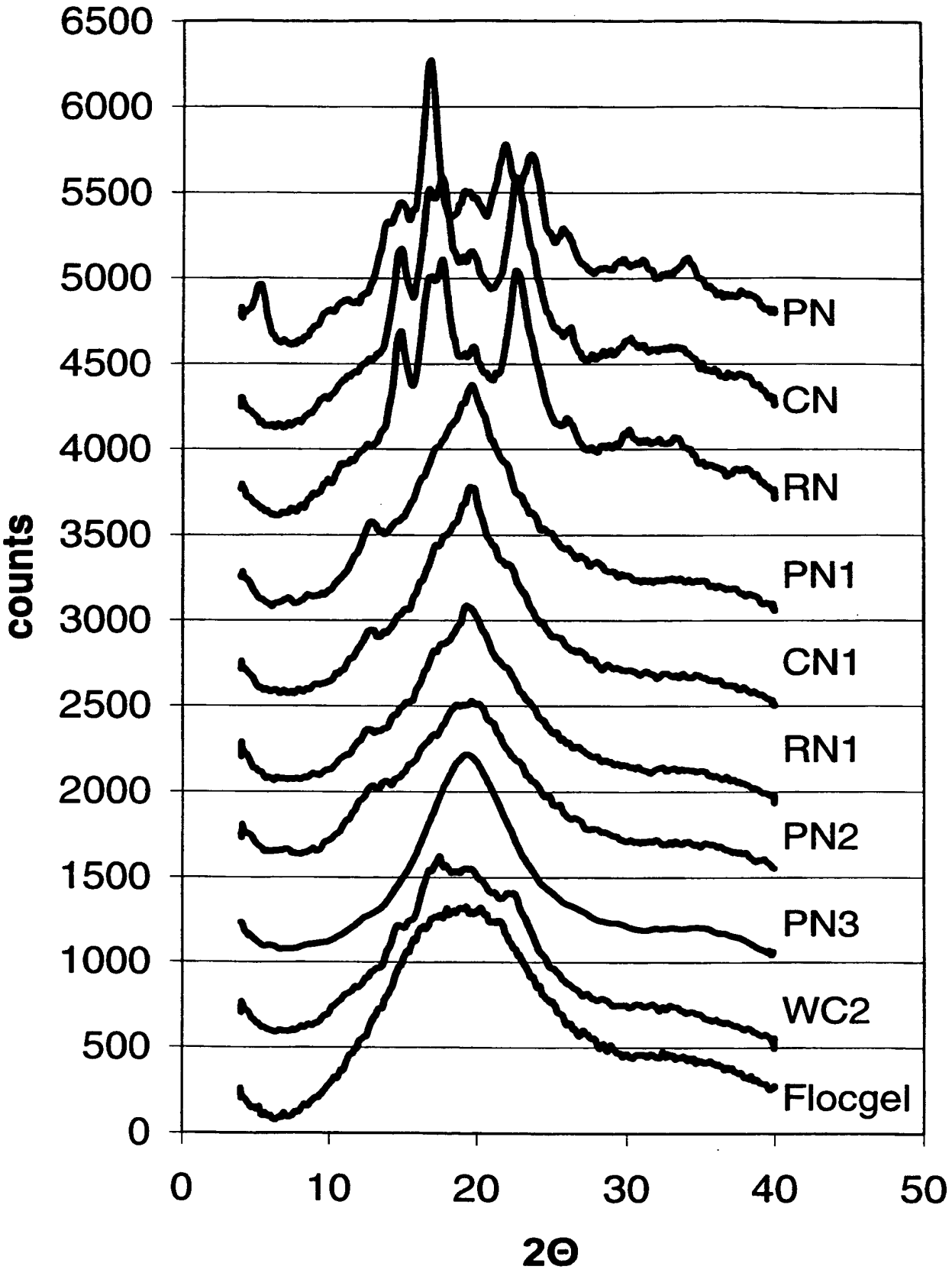
32. Surgical glove according to claim 31

characterized in that the low-cristalline starch has a V-type crystal structure.

33. Surgical glove according to claim 31, 31 or 32 **characterized in that** the birefringence of the modified starch is less than 30%, preferably less than 20%, more preferably less than 10%, and most preferably less than 5% of native starch.

34. Surgical glove according to any of the claims 30-33 **characterized in that** less than 75% of the modified starch is soluble in cold water.

35. Surgical glove according to any of the preceding claims 30-34 **characterized in that** the modified starch is preferably modified potato starch, modified corn starch, modified rice starch, or modified waxy corn starch.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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/NL 00/00294

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B19/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 143 109 A (STOCKUM) 6 March 1979 (1979-03-06) column 3, line 4-22,43-59 column 4, line 21-50; figure 4; example 1	1,2,5,7, 8,11, 13-15, 18,19, 21,22
X	US 5 385 608 A (FITT ET AL.) 31 January 1995 (1995-01-31) abstract column 2, line 65 -column 3, line 53 column 4, line 9-17 column 6, line 42 -column 7, line 16	1,23-25, 29,30,35

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2000	21/08/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/NL 00/00294

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropnate, of the relevant passages	Relevant to claim No.
A	US 5 563 241 A (BEEZHOLD) 8 October 1996 (1996-10-08) cited in the application abstract; claim 1	1,2,8,18
A	US 5 691 446 A (DOVE) 25 November 1997 (1997-11-25) cited in the application abstract	1,2,8,18
A	US 5 037 929 A (RAJAGOPALAN ET AL.) 6 August 1991 (1991-08-06) cited in the application the whole document	26-29, 31-34

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 00/00294

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4143109 A	06-03-1979	NONE	
US 5385608 A	31-01-1995	US 5346892 A	13-09-1994
		US 5126334 A	30-06-1992
		BR 9301423 A	05-10-1993
		CA 2093058 A	04-10-1993
		JP 1993921 C	22-11-1995
		JP 6239901 A	30-08-1994
		JP 7023401 B	15-03-1995
		AT 137506 T	15-05-1996
		AU 634947 B	04-03-1993
		AU 8837191 A	11-06-1992
		BR 9105265 A	18-08-1992
		CA 2056939 A,C	06-06-1992
		CN 1063115 A,B	29-07-1992
		DE 69119205 D	05-06-1996
		DE 69119205 T	14-08-1996
		DK 489424 T	12-08-1996
		EP 0489424 A	10-06-1992
		ES 2086463 T	01-07-1996
		FI 915722 A	06-06-1992
		HK 166196 A	13-09-1996
		JP 2110722 C	21-11-1996
		JP 4293902 A	19-10-1992
		JP 8016122 B	21-02-1996
		KR 191969 B	15-06-1999
		MX 9102354 A	01-06-1992
		NZ 240743 A	25-11-1992
		SG 49076 A	18-05-1998
		ZA 9109340 A	30-12-1992
US 5563241 A	08-10-1996	NONE	
US 5691446 A	25-11-1997	CA 2227753 A	06-03-1997
		CN 1200132 A	25-11-1998
		EP 0846140 A	10-06-1998
		JP 11507413 T	29-06-1999
		WO 9708228 A	06-03-1997
		US 5741885 A	21-04-1998
US 5037929 A	06-08-1991	AU 641275 B	16-09-1993
		AU 8407491 A	17-03-1992
		EP 0544754 A	09-06-1993
		JP 6501277 T	10-02-1994
		WO 9203063 A	05-03-1992